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Synthesis, computational studies and enzyme inhibitory kinetics of substituted methyl[2-(4-dimethylamino-benzylidene)-hydrazono)-4-oxo-thiazolidin-5-ylidene]acetates as mushroom tyrosinase inhibitors

Pervaiz Ali Channar [a], Aamer Saeed [a,*], Fayaz Ali Larik [a], Muhammad Rafiq [b], Zaman Ashraf [c,*], Farukh Jabeen [d,e], Tanzeela Abdul Fattah [a]

[a] Department of Chemistry, Quaid-i-Azam University, 45320 Islamabad, Pakistan
[b] Department of Biochemistry & Biotechnology (Baghdad-ul-Jadeed Campus), The Islamia University of Bahawalpur, Bahawalpur, Pakistan
[c] Department of Chemistry, Allama Iqbal Open University, Islamabad 44000, Pakistan
[d] Florida Center of Heterocyclic Compounds, University of Florida, Gainesville, Fl 32601, USA
[e] Center for Computationally Assisted Science and Technology, North Dakota State University, Fargo, ND 58102, USA

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ABSTRACT

The present article describes the synthesis and enzyme inhibitory kinetics of methyl[2-(arylmethylene-hydrazono)-4-oxo-thiazolidin-5-ylidene]acetates **5a**–**j** as mushroom tyrosinase inhibitors. The title compounds were synthesized via cyclocondensation of thiosemicarbazones **3a**–**j** with dimethyl but-2-yne-dioate (DMAD) **4** in good yields under solvent-free conditions. The synthesized compounds were evaluated for their potential to inhibit the activity of mushroom tyrosinase. It was unveiled that compounds **5i** showed excellent enzyme inhibitory activity with IC_{50} 3.17 μM while IC_{50} of standard kojic acid is 15.91 μM. The presence of heterocyclic pyridine ring in compound **5i** play important role in enzyme inhibitory activity as rest of the functional groups are common in all synthesized compounds. The enzyme inhibitory kinetics of the most potent derivative **5i** determined by Lineweaver-Burk plots and Dixon plots showed that it is non-competitive inhibitor with *Ki* value 1.5 μM. It was further investigated that the wet lab results are in good agreement with the computational results. The molecular docking of the synthesized compounds was performed against tyrosinase protein (PDBID 2Y9X) to delineate ligand-protein interactions at molecular level. The docking results showed that the major interacting residues are His244, His85, His263, Val 283, His 296, Asn260, Val248, His260, His261 and Phe264 which are located in active binding site of the protein. The molecular modeling demonstrates that the oxygen atom of the compound **5i** coordinated with the key residues in the active site of mushroom tyrosinase contribute significantly against inhibitory ability and diminishing the human melanin synthesis. These results evident that compound **5i** is a lead structure in developing most potent mushroom tyrosinase inhibitors.

1. Introduction

Thiazolidin-4-ones is important scaffold in heterocyclic chemistry and the thiazolines ring is present in many pharmacological active substances. Thiazolines derivatives have a great deal of interest owing to their biological activities, such as anti-tuberculosis,[1] anti-convulsant,[2] and fungistatic[3] activities as well as inhibitory activity of gastrointestinal proliferation.[4,5] The five membered *S*- and *S*,*N*-heterocycles were synthesized by reacting dimethyl acetylenedicarboxylate (DMAD) with esters and amides of dithiocarboxylic acids.[6,7] Thioureas react with DMAD to give 1:1 adducts with loss of methanol.[8] A number of other more convenient methods have been reported for the preparation of thiazolidinone derivatives. For example, the reaction of thioamides or thiosemicarbazide derivatives with dialkylacetylenedicarboxylates is an effective method to prepare 2-amino-5-methoxycarbonyl-thiazolidin-4-ones.[9,10] Also, 2-(dimethylamino)-thiazole reacted with DMAD to produce a pyridine derivative *via* extrusion of a sulfur atom.[11] In recent years, the use of microwave irradiation has become popular among synthetic organic chemists, both to improve classic organic reactions (shortening reaction times and/or improving yield), and to promote new reactions.[12] Aly et al.

* Corresponding authors.
E-mail addresses: asaeed@qau.edu.pk, aamersaeed@yahoo.com (A. Saeed), mzchem@yahoo.com (Z. Ashraf).

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demonstrated a very convenient procedure to synthesize 1,3-thiazines by the reaction of but-2-ynedioic acid, propynoic acid ethyl ester, and (*E*)-1,4-diphenyl-but-2-ene-1,4-dione with aroyl-substituted thioureas in acetic acid.[13] The same group changed the conditions of the reaction by mixing a solution of DEAD and aroylthioureas together with triphenyl phosphine.[14] The products were identified as methyl-(2*Z*)-2-[(2*Z*)-2,3-diaryl-carbonylimino-4-oxo-thiazolidin-5-ylidene]-acetates. Acylthiosemicarbazides represent versatile synthon for various syntheses of nitrogen–sulfur heterocycles. The acylthiosemicarbazide moiety provides an opportunity to perform cyclocondensations as well as addition-cyclization reactions. The products of these reactions are thiazin-2-ylidene,[15] thiazoline,[16] triazole,[17] and imidazolidine derivatives.[18,19] It has been reported that the reaction of dimethyl acetylenedicarboxylate with thiocarbamides led to 4-oxathiazolidine derivatives.[20]

Owing to biological importance of the thiazolidinones we here describe the synthesis of title thiazolidinones **5a–j** by condensation of thiosemicarbazones with dimethyl acetylenedicarboxylate. The presence of the thiazolidinone pharmacophore as reported in previous studies, led us to investigate their mushroom tyrosinase inhibitory kinetics of the synthesized compounds. The computational molecular docking studies has also been performed to compare the wet lab results with dry lab findings.

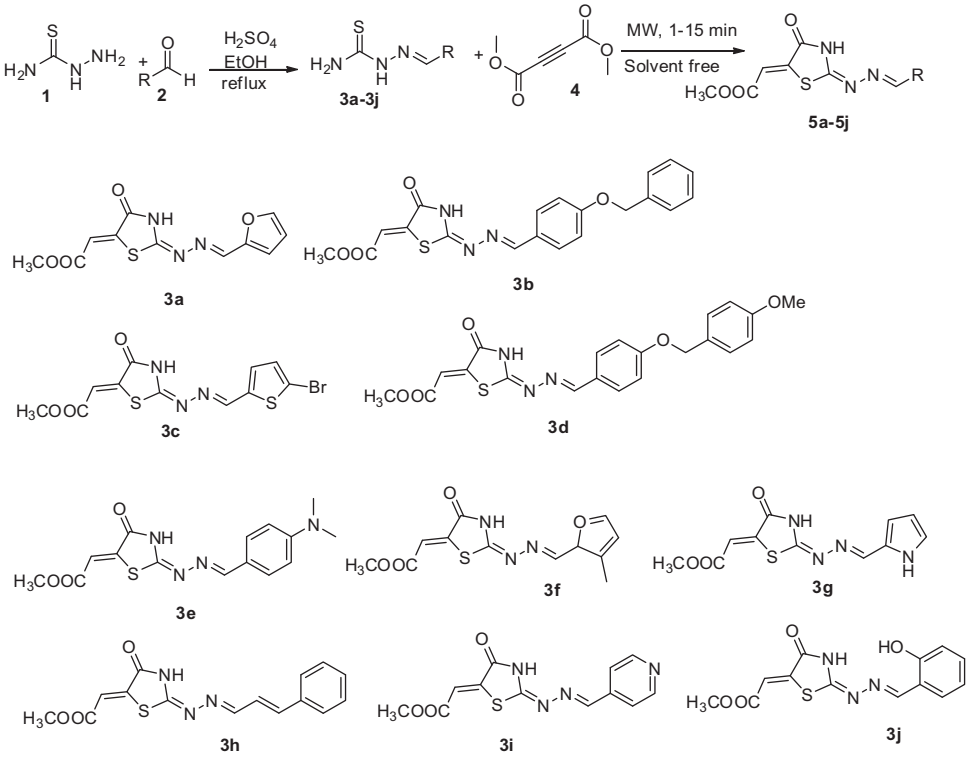
2. Results and discussion

2.1. Chemistry

Thiazolidinone derivatives **5a–j** were synthesized by condensation of substituted thiosemicarbazones **3a–j** with dimethyl acetylenedicarboxylate **4**. Thiosemicarbazones **3a–j** were synthesized as intermediates by acid catalyzed condensation of thiosemicarbazide with a range of substituted aromatic aldehydes (Scheme 1). Thiosemicarbazones **3a–j** were then reacted with dimethyl acetylenedicarboxylate **4** in the absence of any solvent or catalyst, afforded thiazolidinones **5a–j** in good to excellent yields (Scheme 1). DMAD is a highly electrophilic reagent and widely employed as a dienophile in cycloaddition reactions, such as the Diels–Alder reaction and behaving as Michael acceptor in organic transformations. The structures of **5a–j** were assigned on the basis of their FTIR, ^{1}H and ^{13}C NMR spectral data. In the ^{1}H NMR spectra of **5a–j**, the down-field singlets in the region δ 13.04–8.06 ppm were assigned to NH ring proton, while the azomethine protons (C^{2}thiazolH=N) appeared in the region δ 9.38–7.49 ppm. The olefinic protons (CH=C) resonated in the region δ 6.73–6.42 ppm, while the singlets in the region δ 3.90–3.78 ppm were attributed to the protons acetoxy group. In the ^{13}C NMR spectra, carbonyl carbon atoms of the thiazole ring and the acetoxy group appeared in the regions δ 174.0–170.1 ppm and δ 168.5–164.5 ppm respectively, whereas C-2 of the thiazolidinone ring resonated in the region δ 159.4–156.3 ppm. The presence of the signals in the region δ 149.6–145.2 ppm were assigned to azomethine carbon atoms attached to the aromatic rings (ArCH=N), except those of compounds **5a** and **5i** which appeared at δ 160.3 and158.4 ppm, respectively. Olefinic carbon atoms (Cthiazol^{5}=CH) were observed in the region δ 143.9–137.9 ppm, while C-5 of the thiazolidinone ring appeared in the region δ 134.6–131.1 ppm.

2.2. Tyrosinase inhibitory activity

The synthesized thiazolidinones 5**a–j** have been screened for their inhibitory effects on mushroom tyrosinase activity. The compound **5i** showed excellent tyrosinase inhibitory activity with IC_{50} value 3.17 μM while IC_{50} value of standard kojic acid is 15.91 μM. The presence of heterocyclic pyridine ring in compound **5i** play important role in enzyme inhibitory activity as rest of the functional groups are common in all synthesized compounds Table 1.



Scheme 1. Synthesis of 1-(Substituted benzylidene thiosemicarbazides **3a–j.**